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Efficacy of *Centella asiatica* on mitigating temporomandibular pain and improving functionality: a randomized, double blind, pilot clinical trial

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Abstract

Objective To determine the efficacy of *Centella asiatica* extract, ECa233, on alleviating pain symptoms and functional improvement of acute temporomandibular disorders (TMD).

Materials and methods A randomized, double-blind, placebo-controlled, pilot clinical trial was performed using 23 adults with acute TMD. They were randomly assigned into four treatment groups, an ibuprofen (positive control) group, two test groups of ECa233 each of 250 mg, and 500 mg extracts, and a placebo (negative control) group. All subjects were requested to self-administer the test/control capsules, twice a day for 14 days. The pain intensity score, range of mandibular motion and tenderness of the masticatory muscles and temporomandibular joint (TMJ) were recorded at baseline, 7- and 14-days post-treatment.

Results One week after intervention, the pain intensity score significantly decreased in participants receiving 500 mg of ECa233 ($P=0.016$), as well as the placebo group ($P=0.030$) but not in the other groups. Additionally, those receiving 500 mg of ECa233 displayed the highest percentage reduction in self-reported pain intensity and pain on TMJ palpation compared with the other groups ($P>0.050$). On day 14, there were no significant differences observed among the evaluated parameters in the four groups.

Conclusions The orally administered ECa233 has the potential to induce rapid, short term, dose-dependent analgesia in individuals with TMD pain. However, longer-term RCT with a larger cohort is necessary to confirm these findings.

Clinical relevance ECa 233 at 500 mg has the potential to induce a more rapid analgesic response in individuals with acute TMD after a 7-day period.

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Trial registration This trial was registered on the ClinicalTrials.gov, the number is NCT06231212, date of registration: 30/01/2024.

Keywords *Centella asiatica*, Temporomandibular disorders, Pain intensity score, Mouth opening distance

Introduction

Temporomandibular disorders (TMD) are a group of more than 30 conditions that causes pain and dysfunction in the temporomandibular joint. The most recent meta-analysis of the global prevalence of temporomandibular disorders (TMDs) indicates that the incidence of TMDs in the worldwide population is 34%, whereas the rate in Asia is 33% [1]. The significant prevalence of TMD events in the community emphasizes the importance of this disease entity. It signifies a significant economic and social issue.

There are numerous causes for TMD and recent data indicate genetic constitution, life stressors, pain sensitivity may play a role in its aetiology. These disorders commonly lead to functional impairment of the masticatory musculoskeletal system [2]. TMD clinical signs and symptoms can be divided into pain and dysfunction according to structures that affect the masticatory muscles and the temporomandibular joint (TMJ) [3].

The conservative management of TMD is the preferred choice of clinicians and it generally entails patient education and self-care instructions, pharmacotherapy and provision of intraoral appliances, depending on the clinical presentation [4, 5]. However, of these, the pharmaceutical intervention, mainly non-steroidal anti-inflammatory drugs (NSAID) remains as the mainstay, popular management modality to promote rapid healing and ameliorate discomfort and pain. Nevertheless, the common NSAID such as Ibuprofen and its derivatives have adverse gastro-intestinal side effects particularly on long term use with resultant poor patient compliance and treatment failure [6, 7]. Hence alternative therapeutic procedures are required and anti-inflammatory herbal compounds may constitute an effective such option.

ECa233 is a standardized plant extract of *Centella asiatica* and this compound has been shown to reduce pain for oral afflictions [8]. The extract ECa233 contains triterpenoid glycosides not less than 80% and the ratio between madecassoside and asiaticoside should be 1.5 ± 0.5. ECa233 has been demonstrated to possess anti-inflammatory and antinociceptive properties in acute inflammatory lesions and erythema. For example, in a recent study, we demonstrated the efficacy of an oral paste containing 0.05% ECa233 in reducing pain, ulcer size and erythema in a cohort of Thai patients with recurrent oral aphthae, within a period of 10 days [9]. Moreover, others have shown that 0.05% ECa 233 gel formulation improved human skin erythema due to laser treatment [10]. Additionally, we have shown in an in vivo study of mice that ECa 233 significantly mitigates temporomandibular joint osteoarthritis by modulating the expression of local inflammatory mediators [11].

Hence the aim of this randomized, double blind, pilot clinical trial was to determine the efficacy of ECa233 on pain reduction and functional improvement of temporomandibular joint in subjects with acute pain symptoms associated with TMD. For the purpose of assessing the main outcomes, pain intensity levels and mandibular range of motion (pain-free, unassisted and assisted mouth opening) were recorded at baseline and 7- and 14-days post-intervention. Masticatory muscle and jaw joint tenderness were evaluated by palpation by a trained clinician according to the Diagnostic Criteria for TMD (DC/TMD) [3]. The null hypothesis was that at baseline, seven days, and fourteen days after the intervention, there would be no discernible differences in the mandibular range of motion and pain intensity levels between TMD patients receiving ECa233, a placebo, or ibuprofen.

Materials and methods

Subjects and inclusion criteria

This study protocol was approved by the Human Research Ethics Committee of the Faculty of Dentistry, Chulalongkorn University (project code: HREC-DCU:2019-090; date of approval: 4/17/2020) and complied with the Declaration of Helsinki. All subjects provided informed consent permission prior to study participation. This trial was registered on the ClinicalTrials.gov (http://clinicaltrials.gov), the number is NCT06231212, date of registration: 30/01/2024.

Firstly, subjects with TMD were screened at the Occlusion and Orofacial Pain Clinic at Chulalongkorn University Dental Hospital, and then recruited for this double-blind, randomized, placebo- and active-controlled clinical study. Inclusion criteria include subjects between the ages of 18 and 50 years, reporting TMD pain lasting for 30 days or less (acute pain), with pain ratings between 5 and 8 on a 0–10 numeric rating scale. The pain scale used ranges from 0, representing no pain, to 10, representing severe pain, with 1–3 indicating mild pain, 4–6 moderate pain, and 7–10 severe pain.

Participants who self-reported sleep bruxism or had any underlying chronic disease or undergoing any sort of treatment that may influence pain perception and/or inflammation, including diabetes, psychological distress, systemic inflammatory disorders, oral appliances, and medications were excluded.

After enrollment, all subjects were diagnosed into two categories: the first group with muscle pain and the second with both muscle and TMJ pain according to DC/TMD axis I protocol [3, 12]. Then, the subjects received standard TMD self-care instructions [13] and received a pre-prepared, sealed, opaque packet containing the randomly allocated treatment groups. They were randomly allocated into four groups: (1) negative control group of 6 patients receiving a daily dose of 1,000 mg of lactose (placebo group); (2) positive control group of 5 patients taking a daily dose of 800 mg of ibuprofen (ibuprofen group); (3) the first ECa233 intervention group of 6 patients taking a daily dose of 250 mg of the active compound (ECa250 group) and (4) the second ECa233 intervention group of 6 patients taking a daily dose of 500 mg of ECa233 (ECa500 group). The active ingredients in the ECa capsules were pharmaceutical grade and sourced from Siam Herbal Innovation Ltd. (Lot No. MRA051401).

All subjects were requested to take the capsules of ECa233 twice a day in the morning and evening, after meals for 14 days. All capsules shared identical shape and color, manufactured in compliance with standard medical regulations and requirements, and successfully passed analytical tests conducted by Pharma Nueva Co., Ltd. They were stored at room temperature until prescribed. An identical lot of capsules were used throughout the experimental period.

The software G*Power 3.1.9.7 was used to analyze the sample size. An F-test (ANOVA, fixed effects, omnibus, one-way) was conducted, resulting in an effect size of 0.8. With an alpha error of 0.05, a power of 0.80, and four groups, the total sample size required was determined to be 24. As a result, six participants were established for each group.

Assessment of outcome variables via questionnaires and clinical examination

The self-reported pain intensity levels and other clinical parameters were collected at 3 time points: pre-intervention (baseline), 7- and 14-days post-intervention. The pain intensity score was determined by using a 10-point ordinal scale (0 representing no pain and 10 indicating severe pain). The clinical examination included the recording of the mandibular range of motion (ROM) in millimeters and the number of painful areas. These areas were evaluated upon palpation by a trained and calibrated senior clinician (P.P.) according to the DC/TMD criteria [3, 12].

A total of three mandibular ROM parameters were measured at pain-free, unassisted, and assisted mouth opening. Unassisted mouth opening was measured at the maximum distance regardless of pain or discomfort, whereas assisted mouth opening was performed with the assistance of the clinician. Afterwards, three further measurements were performed for each participant using a graduated metric ruler from the incisal edge of the right maxillary to mandibular central incisors.

Finally, the number of masticatory muscles and TMJs with pain upon palpation were quantified on both the left and the right side by the same calibrated examiner (initials). The total score of muscle pain was evaluated in the following locations using anatomical landmarks [3], temporalis muscles, masseter muscle, lateral pterygoid muscles, as well as the muscles around the posterior mandibular and submandibular region. Whereas the total score for TMJ pain was evaluated at the lateral pole of condyle.

Statistics

All data were tested for normality using the Shapiro-Wilk test. Data is presented as a mean ± standard deviation (SD), median and interquartile range (IQR) using the SPSS software (version 22, IBM, NY, USA). The Kruskal Wallis H test was used to analyze statistical significance between controls (placebo and active) and intervention groups. The Bonferroni correction was implemented. The Wilcoxon signed-rank test was used to evaluate the data within each group at 95% confident interval. The significance level was set at 5%.

Results

A total of 23 subjects (8 males and 15 females) with a mean age of 26.35 ± 4.99 years (range 18–36 years) and having TMD and fulfilling the inclusion and exclusion criteria of the study were enrolled in the study. The consort flow chart of the study is provided in Fig. 1. The demographic data and the baseline characteristics of all four separate groups of participants are shown in Table 1.

Efficacy of ECa 233 in mitigating pain intensity

There was no significant difference in the baseline pain intensity levels of all four groups ($P > 0.0125$). On the first evaluation 7 days after treatment initiation there was a significant reduction in the pain intensity in both the ECa500 group ($P = 0.016$) as well as the placebo group ($P = 0.030$) compared with pretreatment levels (Fig. 2). The highest percentage reduction in pain intensity from baseline was noted in the ECA500 groups (66.11%). Interestingly, at 14 days posttreatment, all groups had a reduction in pain intensity compared to pre-treatment levels, though there was no significant difference in this parameter between the four groups (Fig. 2).

Efficacy of ECa 233 in reducing areas of pain upon palpation

There were no significant differences in the number of muscles or the TMJ tender points at 7- and 14- days post-treatment in all groups (Figs. 3 and 4). However, the most

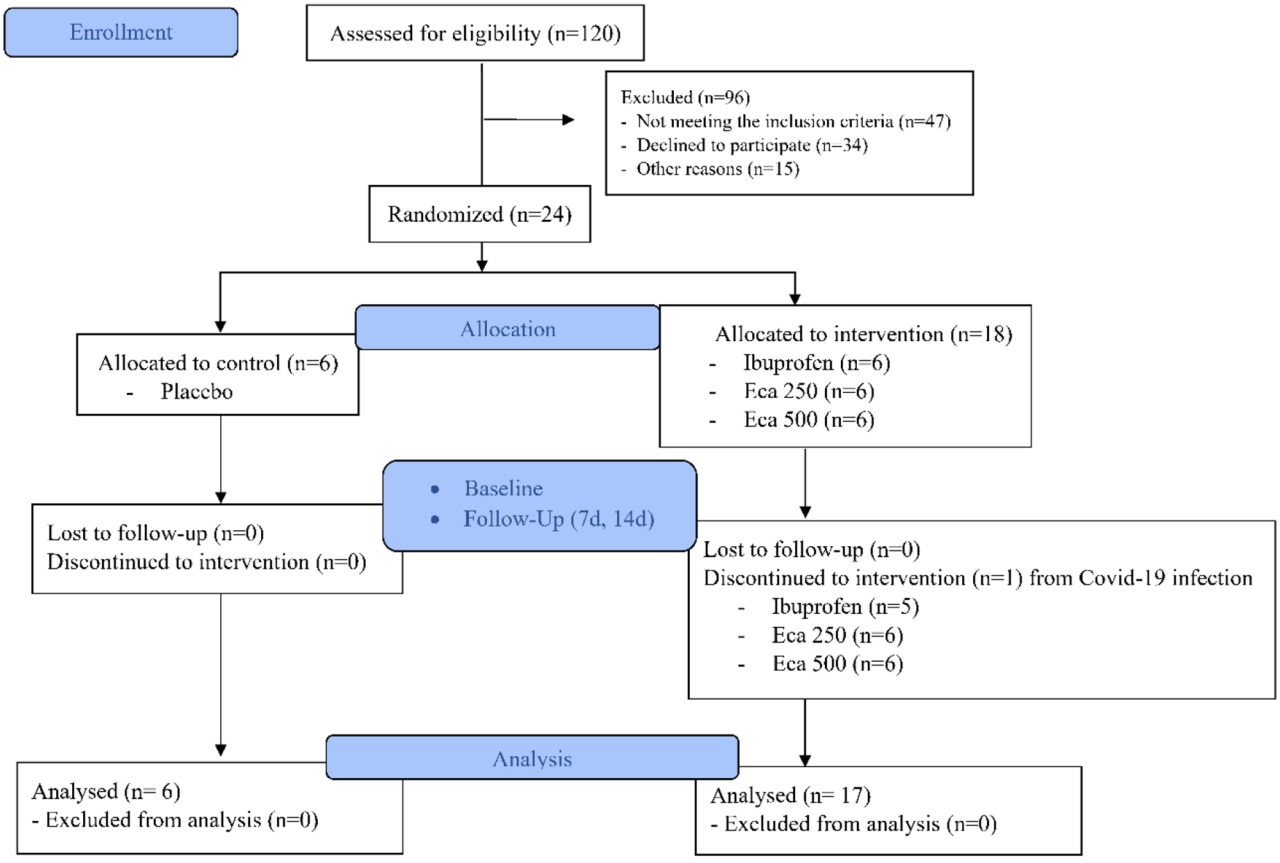

Fig. 1 Consort flow diagram of the study

Table 1 Demographic data and baselines characteristics of all recruited participants (*N* = 23)

Characteristics	**Overall**	**Treatment approaches**			
		Placebo (*N*=6)	**Ibuprofen (*N*=5)**	**ECa250 (*N*=6)**	**ECa500 (*N*=6)**
Age (years): mean (±SD)	26.35 (±4.99)	24.00 (±3.85)	24.20 (±3.20)	29.17 (±4.62)	27.67 (±6.53)
Sex (%): Male	34.78	16.67	0.00	50.00	66.67
Female	65.22	83.33	100.00	50.00	33.33
Clinical diagnosis					
Muscle pain	4	1	1	1	1
Muscle and TMJ pain	19	5	4	5	5
Patient-reported outcome at baseline: median (IQR)					
Pain score (ranges 0–10)	5 (1.5)	6 (2)	6 (1)	5 (0.75)	5.5 (1)
Range of motion at baseline: mean (±SD)					
Pain-free mouth opening distance (mm)	30.22 (±10.07)	29.00 (±7.87)	25.80 (±11.95)	28.17 (±9.91)	37.17 (±9.37)
Maximum unassisted mouth opening distance (mm)	40.17 (±9.57)	39.83 ± (7.20)	36.00 (±12.53)	41.67 (±11.55)	42.50 (±8.09)
Maximum assisted mouth opening distance (mm)	44.35 (±8.36)	44.00 ± (5.59)	39.60 (±11.55)	47.83 (±9.56)	45.17 (±6.37)
Number of tender muscles and TMJs: median (IQR)					
Pain on muscle palpation (10 locations)	3 (3)	3.5 (2.5)	3 (4)	2 (0.75)	4 (5.25)
Pain on TMJ palpation (2 locations)	1 (0)	1 (0)	1 (1)	1 (0)	1 (0.75)

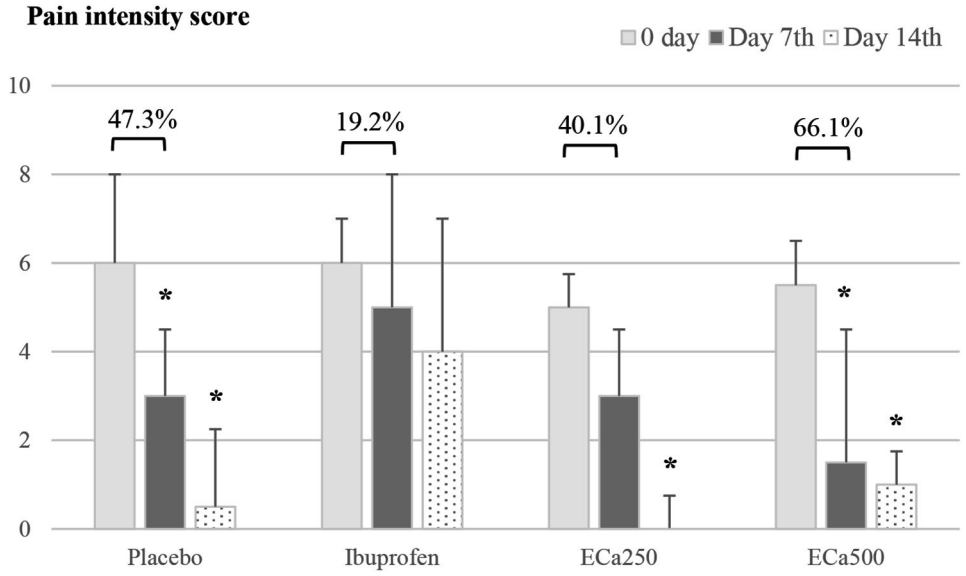

Fig. 2 Pain intensity scores between baseline, and 7 days and 14 days post-treatment. All values are displayed as median (IQR). The percent change of pain intensity score at 7 days post-treatment compared to baseline is illustrated. * Significant differences ($P < 0.05$) in pain intensity between day 0 and either day 7 or day 14, in each group are asterisked (Wilcoxon signed-ranks test)

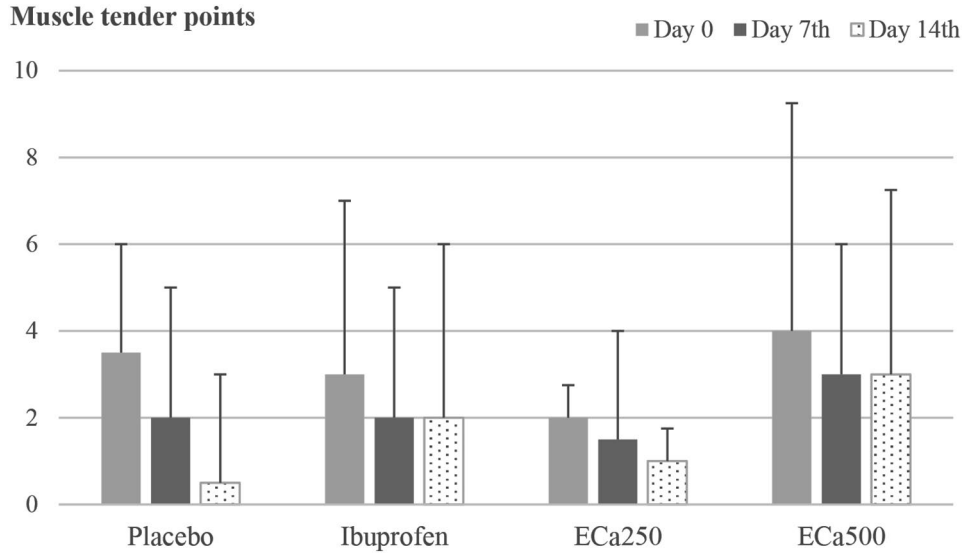

Fig. 3 Number of masticatory muscles tender points at baseline, 7 days and 14 days post-treatment. All values are displayed as median (IQR) and p-values taken from Wilcoxon signed-rank test

percentage reduction in TMJ tender points was found in the ECa500 group, 7-days posttreatment (Fig. 4).

Efficacy of ECa 233 and jaw function

There was no significant difference in the mandibular range of motion, including pain-free, unassisted and assisted mouth opening, between baseline, and at 7- and 14- days posttreatment in all groups (Fig. 5).

Discussion

Temporomandibular disorders may be precipitated by a diversity of causes, and they present with major symptoms such as pain, stiffness and restriction in jaw opening. Of these, pain is the commonest presenting symptom and the main driving force for the search for treatment. Here we attempt to evaluate the effect of ECa 233 on the pain amelioration in a Thai cohort with acute pain due to TMD.

Within the limitations of the study, we have demonstrated that pharmacological intervention by

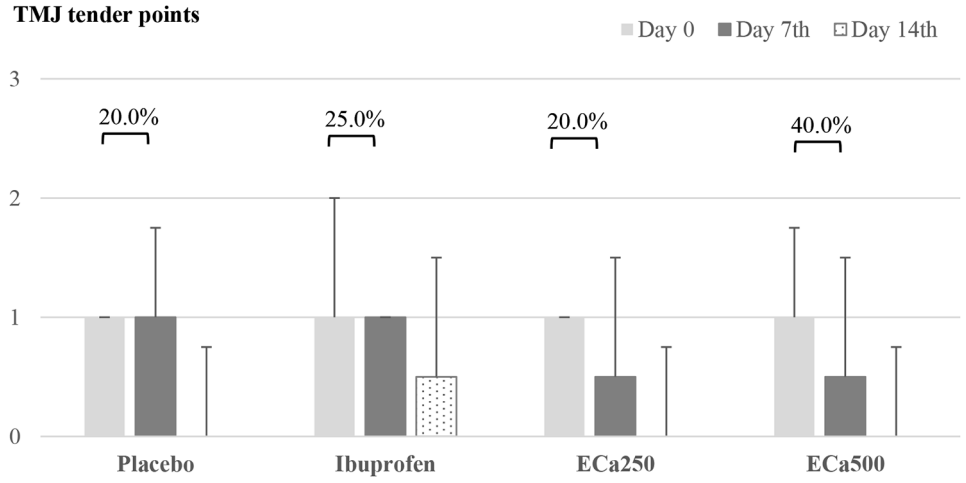

Fig. 4 Number of TMJ tender points at baseline, 7 days and 14 days post-treatment. All values are displayed as median (IQR) and p-values taken from Wilcoxon signed-rank test. The percent change of TMJ tender points at 7 days post-treatment compared to baseline is illustrated

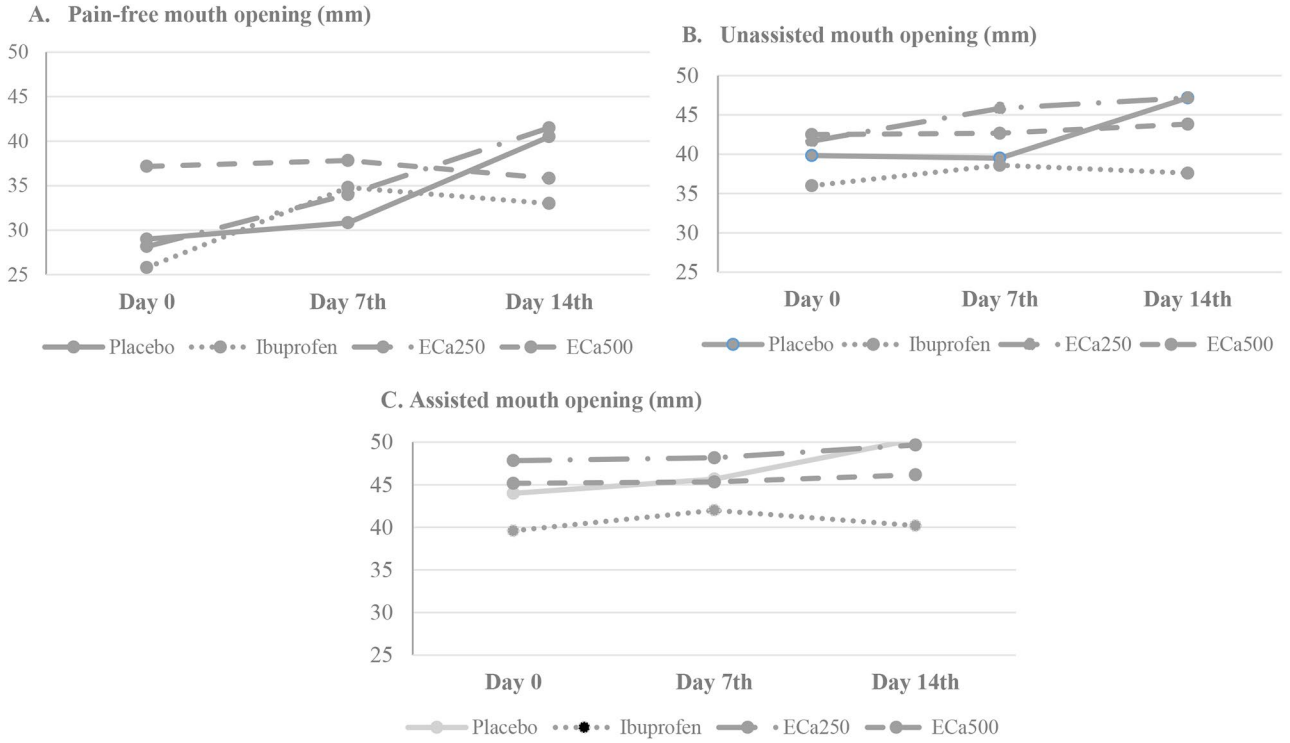

Fig. 5 Range of mouth opening at baseline, 7 days and 14 days post-treatment. All values are displayed as mean ± SD using Wilcoxon signed-rank test. No significant differences were noted between pre-treatment and post-treatment for all three parameters, i.e. pain-free mouth opening (**A**), unassisted mouth opening (**B**) and assisted mouth opening (**C**)

administration of ECa 233 may be useful for relieving acute pain of TMD at least for a short period. Thus, although all participants exhibited a reduction in pain intensity as well as total regions with pain on palpation, 14-days posttreatment, those who received high dose ECa233 (500 mg) exhibited the most percentage reduction in pain intensity and TMJ tenderness at 7-days posttreatment. Moreover, no subjects experienced any discomfort or unwanted side effect of ECa 233 during the period of treatment.

The mechanisms of TMD pain and the nociceptive pathways are incompletely understood, although it is known that pain may either be muscular and/or joint in origin. It is known that during the acute phase of TMD, hard and soft tissue damage leads to release of a wide variety of inflammatory and nociceptive mediators resulting in local and referred pain [14]. In patients with

painful TMD, it is crucial to control this symptom as part of the initial management before pursuing other treatment modalities, such as the provision of an oral appliance. Analgesic drugs, such as NSAIDs, are the current treatment of choice for the condition, although past work has consistently failed to show differences between the latter over placebos [15, 16]. For instance, in a Cochrane analysis of 11 studies the authors concluded that there is insufficient evidence to support or not support the effectiveness of the reported drugs for the management of pain due to TMD. Moreover, the therapy of TMD with NSAIDs is a temporary, stop gap measure as both clinicians and patients are concerned about the risks of the anti-inflammatory medications. Hence, searching for alternative pharmaceutical modalities is an important endeavor.

Although the data from our study was equivocal and showed no differences in pain intensity or muscle tenderness between the placebo and test groups at day 14 post-intervention, we noted the highest percentage reduction in pain intensity in the ECa500 group, implying that the drug may have a salutary pain-relieving effect. These findings are similar to the analgesic effect of ECa233 we noted in a previous study where an oral paste with the drug was effective in reducing pain, erythema and inflammatory response of minor aphthous ulcers [11]. Others too have shown an anti-inflammatory effect of ECa233 in animal studies. It is therefore tempting to speculate that the pain reduction associated with ECa233 extract may be due to an associated, concomitant reduction in the localized inflammatory response. Damkerngsuntorn et al., for instance, showed in a mouse model ECa233 significantly reduces the expression of inflammatory mediators including TRPV1, ASIC3, TNF-α, IL-1β in a TMJ osteoarthritis model [13]. Indeed, these molecular biomarkers, including TNF-α, IL-1β, are found to be involved with painful TMD [17, 18]. Intriguingly in this context, a recent in vivo study revealed an inverted U-shaped dose response relationship of ECa233 treatment on spatial memory performance [19], suggesting that beneficial effects of ECa233 may be seen at very specific therapeutic doses.

As for the reduction in the total areas of pain on palpation and the range of mouth opening, we did not observe a significant difference between the ECa233 test group and the placebo groups after 14 days. However, the largest percentage reduction in tender points of TMJs was found in the ECa500 group at 7-days post-treatment. The self-care instructions provided to all participants may have had a positive effect on time-related symptom relief in this context [20]. It is generally accepted that chronic painful TMD are strongly influenced by psychosocial factors [21, 22]. However, the confounding role of such factors was not evaluated in our study.

This study has some limitations. First, we did not categorize or stratify participants into different subgroups such as those with muscle or joint origin of pain because of the limited sample size. Second, since this is a pilot study, we only investigated the pain outcomes 14 days post-therapy. Given the relatively chronic nature of the disease, a long-term RCTs assessing the potential impact of ECa233 on TMD pain is warranted. Additionally, further data on the dosage and toxicity is crucial prior to wider uses of this drug in managing TMD.

Conclusion

Within the limitations of this preliminary study, we have demonstrated that oral administration of ECa233 is likely to be useful for relieving acute pain of TMD at least for a short period and may therefore be employed as a component of an early pain management strategy in individuals with this condition.

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Author contributions
P.P. and A.W. contributed to conception and design. P.P. participated in data collection, conducted data analysis, interpreted the findings, and drafted and revised the manuscript. A.W. played a substantial role in securing funding and contributed to manuscript revisions. M.H.T contributed to the preparation of ECa233 and provided technical support. R.S. and N.R. were substantially involved in the administrative aspect of the study. L.S. critically evaluated and edited the manuscript. All authors have reviewed and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All subjects provided written informed consent to participate in the study. This study protocol was approved by the Human Research Ethics Committee of the Faculty of Dentistry, Chulalongkorn University (project code: HREC-DCU:2019-090; date of approval: 17/04/2020).

Competing interests
The authors declare no competing interests.

Consent for publicaton
Not applicable.

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